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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,423	07/31/2003	Masaya Tohyama	59150-8023.US00	3705

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EXAMINER	
KOLKER, DANIEL E	
ART UNIT	PAPER NUMBER
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/633,423	TOHYAMA ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,22,24-27 and 263-266* is/are pending in the application.

4a) Of the above claim(s) *24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,22,25-27 and 263-266* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *21,22,24-27 and 263-266* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks and amendments filed 14 December 2006 have been entered. Claims 1 – 20, 23, and 28 – 262 are canceled; claims 21 – 22, 24 – 27, and 263 – 266 are pending.

Election/Restrictions

2. Claim 24 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 25 July 2005.

3. Claims 21 – 22, 25 – 27, and 263 – 266 are pending and under examination.

Withdrawn Rejections and Objections

4. The following objections and rejections set forth in the previous office action are withdrawn:

A. The objection to claim 28 is moot as the claim is now canceled.

B. The objections to claims 21 and 25 are withdrawn in light of the amendments.

C. The rejections under 35 USC 102(e) or in the alternative under 103(a) over Bredensen are withdrawn in light of the amendments. Whereas the previous claims allowed for unlimited numbers of possible substitutions, insertions, and deletions, the amended claims now require SEQ ID NO:2 or a protein that has one to five amino acid insertions, deletions, or substitutions. Bredensen does not teach such a protein.

Maintained Rejections and Objections

Priority

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. Receipt is also acknowledged of the certified translation of the Japanese priority document, said translation filed 14 December 2006.

6. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35

U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, priority document 2003-092923 (Japan), fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The examiner is unable to find support for agents comprising "a PTD domain" as recited in independent claims 21 and 27 in the translation of the Japanese priority document. Thus for the purposes of applying prior art, the instant claims are granted priority to 30 April 2003, the date parent application 10/427741 was filed. Support for the PTD domain can be found at originally-filed claim 30 of the parent case.

Should applicant disagree with the examiner's factual determination above, applicant should point out how the invention now claimed is fully described in the Japanese priority document. This could be accomplished by pointing out the specific line and page numbers which disclose coupling of a PTD domain to SEQ ID NO:2 as recited in claims 21 and 27.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21 – 22, 25 – 27, and 263 – 266 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

This rejection stands for the reasons of record. While the claims have been narrowed, the specification does not demonstrate possession of the genus of molecules now set forth in the claims. The claims encompass administration of SEQ ID NO:2 "or a sequence derived therefrom by from one to five amino acid substitutions, deletions, and additions which retains biological activity of Pep5". This is a very broad genus. The protein of SEQ ID NO:2 is 15 amino acids long, so the claims allow for deletion of up to one-third of the peptide, wherein the resultant peptide retains "biological activity in an amount effective for regeneration". The specification does not disclose to the artisan which third of the protein can be deleted whereby

any particular activity is retained. The skilled artisan cannot visualize this genus of proteins, because the specification fails to disclose any deletion mutants or substitution mutants which retain the appropriate activity. The specification discloses as single mutant wherein one amino acid is added to one end of SEQ ID NO:2. But the disclosure of two proteins which have the relevant structure and function does not provide evidence of possession of the genus of starting materials for this method, and consequently such a minimal disclosure does not comply with the written description requirement of 35 USC § 112, first paragraph.

An adequate written description of a DNA, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

While the above quotation from Fiers is on point to DNA, the same logic applies to proteins. Here, applicant has provided a plan for obtaining the chemicals, but has not disclosed to the public those elements of the protein which are present in the variants. Thus the skilled artisan could not determine that applicant had in his possession those variants which are now set forth in the method claims. Accordingly, the rejection for lack of written description stands.

Applicant argues, on p. 5 of the remarks filed 14 December 2006, that "one skilled in the art would clearly recognize that the inventors were in possession of the full scope of the claimed genus". The examiner disagrees. Applicant has shown possession of only two members of this genus. One member is SEQ ID NO:2, the other member is SEQ ID NO:2 with a single amino acid added to one end. The specification sets forth no methods of administering any proteins which are deletion or substitution mutants of SEQ ID NO:2 which retain "the biological activity of Pep5" as recited in claims 21 and 27 for example. Note that "biological activity" is defined very broadly in the specification at paragraphs [0472] and [0531] of US 2004/0191240, the publication of this application. The specification does not describe to the artisan which regions of the protein can be deleted such that the relevant biological activity will be retained, and therefore fails to provide evidence of possession of the full scope of the products now claimed.

8. Claims 21 – 22, 25 – 27, and 263 – 266 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition consisting of the

protein of SEQ ID NO:2 with or without a C-terminal alanine, does not reasonably provide enablement for any polypeptide sequence derived therefrom with one to five additions, deletions, and substitutions which retain the biological activity, as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection stands for the reasons of record. Briefly, the specification shows actual reduction to practice of two proteins within the scope of the claims, namely SEQ ID NO:2 itself and SEQ ID NO:2 with a C-terminal alanine. The specification shows both how to make the proteins and how to use them, as they both are able to functionally regenerate nerves. However, what is claimed is considerably broader than this, even given that the claims have been narrowed to only include a maximum of 5 insertions, deletions, or substitutions. The specification discloses no substitution or deletion variants which retain any particular activity. There is no indication as to what regions of the proteins must be retained such that biological activity is maintained. Furthermore, while the specification discloses how to use SEQ ID NO:2 with or without a C-terminal alanine (i.e. for nerve regeneration), the specification does not disclose how to use any protein with "biological activity" as broadly defined. The intended use of the compositions of claims 21 and 27 is for regenerating nerves, but the claims encompass proteins with any biological activity, no matter whether it is related to nerve regeneration or not.

On p. 6 of the remarks, applicant argues that the claims are enabled over their full scope as several assays to determine which biological activity the undisclosed mutants have are described in the specification. While the assays are described, the term "biological activity" is much broader than what is actually disclosed. Furthermore, the specification does not disclose to the artisan how to use those variants which have none of the activities set forth in these assays but are still biologically active as defined. Thus given the breadth of the scope of the claimed protein variants, the breadth of biological activities that said variants might have, and the fact that the specification discloses only two, very closely related proteins which fall within the scope of the claims, the skilled artisan would have to resort to a very large degree of experimentation in order to determine both how to make and how to use the full scope of the compositions claimed. Given the lack of guidance as to which regions of the proteins must be retained in the variants and the breadth of the claims, the very large degree of experimentation required would be undue, consistent with the teachings of Rudinger, previously made of record.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 21 – 22, 25 – 27, and 263 – 266 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ilag in view of Schwarze (1999. Science 285:1569 – 1572), Voet (Biochemistry, Second Edition, 1995. pp. 58 – 59), and Bertin (U.S. Patent Application Publication 2002/0061833, published 23 May 2002, filed 26 December 2000).

This rejection stands for the reasons of record. The reasons why the prior art references meet the limitations of all claims under examination are set forth in the previous office actions and for the sake of brevity will not be repeated herein. Briefly, Ilag teaches the protein of SEQ ID NO:2 and teaches it binds to the intracellular domain of p75. Schwarze teaches fusion proteins comprising PTD domains, specifically the PTD domain from HIV TAT protein and teaches the method is applicable for delivery of any protein. Schwarze even demonstrates the utility of the method in delivering beta-galactosidase, a marker protein, to the brain. Schwarze also teaches that molecules larger than 600 daltons do not enter cells.

It would have been obvious to one of ordinary skill in the art to modify the protein sequence of SEQ ID NO:2 from Ilag et al. by fusing it to the TAT PTD domain, as taught by Schwarze. The motivation to do so is provided by Bertin, is to aid in crossing the cell membrane thereby inhibiting cell death, as Bertin teaches that proteins which bind to the intracellular domain of p75 inhibit cell death. Voet provides the weight of all twenty amino acids that are used in proteins and provides evidence that the protein of SEQ ID NO:2 (i.e. the protein from Ilag) is too large to enter the cell, thereby motivating the artisan to modify the protein from Ilag to allow it to enter cells.

Applicant argues, on p. 9 of the remarks, that although Schwarze provides the teaching which is missing from the prior art reference by Ilag, none of the cited references provide sufficient motivation to modify the protein from Ilag by attaching the PTD domain from Schwarze to it. Applicant's arguments have been fully considered but they are not persuasive. Ilag teaches the protein consisting of the sequence of SEQ ID NO:2 binds to the intracellular domain of p75. Bertin teaches that proteins which bind to the intracellular domain of p75 inhibit cell

death. Thus the artisan would be motivated to have the protein delivered to the intracellular milieu. The reference by Schwarze indicates that those molecules larger than 600 daltons generally do not enter cells readily, and Voet teaches the size of amino acids. Together, these two references would have instructed the artisan of ordinary skill that in order to have the protein from Ilag enter the cell, it would have to be modified. Schwarze then provides instructions to the artisan of ordinary skill as to how to modify the protein, i.e. by attaching a PTD domain as recited in claims 21 and 27. Thus the prior art references provide the motivation to modify the protein from Ilag.

Conclusion

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DK

Daniel E. Kolker, Ph.D.
March 6, 2007

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER